DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

Food and Drug Administration
College Park, MD 20740

OCT 12 2005

Jonathan W. Emord, Esq.
Emord & Associates P.C.
1800 Alexander Bell Drive
Suite 200
Reston, Virginia 20191

RE: Health Claim Petition – Calcium and (1) Kidney Stones; (2) Urinary Stones; and (3) Kidney Stones and Urinary Stones (Docket No. 2004Q-0102).

Dear Mr. Emord:

This letter responds to the health claim petition dated October 9, 2003, submitted to the Food and Drug Administration (FDA or the agency), on behalf of Marine Bio USA, Inc. pursuant to Section 403(r)(5)(D) of the Federal Food, Drug, and Cosmetic Act (the Act) (21 U.S.C. § 343(r)(5)(D)). The petition requested that the agency authorize a health claim characterizing the relationship between the consumption of calcium and a reduced risk of: kidney stones; urinary stones; and kidney stones and urinary stones.

The petition proposed the following model health claims for calcium dietary supplements:

1. Calcium may reduce the risk of kidney stones.
2. Calcium may reduce the risk of urinary stones.
3. Calcium may reduce the risk of kidney stones and urinary stones.

FDA informed you on October 24, 2003, that FDA was not able to acknowledge receipt of the petition and begin its preliminary review of the petition because the petition was not complete. In response, you supplied the needed information in a supplemental submission received by FDA on November 25, 2003. FDA acknowledged the petition in a letter dated December 9, 2003, which initiated FDA's preliminary review of the petition. In that letter, FDA also informed you that the date by which FDA would either file or deny the petition was March 4, 2004.

Based on a preliminary review, FDA determined that the scientific evidence supporting the proposed health claims did not meet the "significant scientific agreement" standard in 21 CFR 101.14(c) which is applicable to dietary supplements. FDA notified you of this decision and you submitted a letter dated March 2, 2004, stating that your client, Marine Bio USA, Inc., chose to seek FDA review of the petition as a qualified health claim. Accordingly, FDA filed the petition on March 16, 2004 as a qualified health claim

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petition and posted the petition on the FDA website for a 60-day comment period, consistent with the agency's guidance for procedure on qualified health claims[1]. In a letter dated June 16, 2004, you notified FDA that Marine Bio Co. Ltd. is now the petitioner of record for this petition, originally submitted by its wholly owned subsidiary, Marine Bio USA, Inc. The initial deadline for FDA's response on the petition was October 27, 2004. After mutual agreement, the deadline for the agency's response was last extended to October 12, 2005.

The agency received two comments from academia, both disagreeing with the petition's contention that calcium intake may lower the risk of kidney stones or urinary stones. These comments concluded that a high calcium intake potentially *increases* the risk of stone formation rather than lowering the risk. You submitted comments opposing this view. FDA considered the relevant comments in its evaluation of this petition.

This letter sets forth the basis of FDA's determination that there is no credible scientific evidence to support the proposed health claims and the reasons the Agency is denying these qualified health claims. Throughout the text of this letter, the amount of calcium is expressed in weight of elemental calcium rather than weight of calcium compounds (e.g., calcium carbonate, calcium citrate).

I. Overview of Data and Eligibility for a Qualified Health Claim

A health claim characterizes the relationship between a substance and a disease or health-related condition (21 CFR 101.14(a)(1)). The substance must be associated with a disease or health-related condition for which the general U.S. population, or an identified U.S. population subgroup is at risk (21 CFR 101.14(b)(1)). Health claims characterize the relationship between the substance and a reduction in risk of contracting a particular disease.[2] In a review of a qualified health claim, the agency first identifies the substance and disease or health-related condition that is the subject of the proposed claim and the population to which the claim is targeted.[3] FDA considers the data and information provided in the petition, in addition to other written data and information available to the agency, to determine whether the data and information could support a relationship between the substance and the disease or health-related condition.[4]

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[1] "Interim Procedures for Qualified Health Claims in the Labeling of Conventional Human Food and Human Dietary Supplements" (July 10, 2003). [http://www.cfsan.fda.gov/~dms/nuttf-e.html]

[2] See *Whitaker v. Thompson*, 353 F.3d 947, 950-51 (D.C. Cir 2004) (upholding FDA's interpretation of what constitutes a health claim), *cert. denied*, 125 S.Ct. 310 (2004).

[3] See guidance entitled "Interim Evidence-based Ranking System for Scientific Data," July 10, 2003. [http://www.cfsan.fda.gov/~dms/hclmgui4.html]

[4] For brevity, "disease" will be used as shorthand for "disease or health-related condition" in the rest of the section.

The agency then separates individual reports of human studies from other types of data and information. FDA focuses its review on reports of human intervention and observational studies.[5]

In addition to individual reports of human studies, the agency also considers other types of data and information in its review, such as meta-analyses,[6] review articles,[7] and animal and *in vitro* studies. These other types of data and information may be useful to assist the agency in understanding the scientific issues about the substance, the disease or health-related condition, or both, but can not by themselves support a health claim relationship. Reports that discuss a number of different studies, such as meta-analyses and review articles, do not provide sufficient information on the individual studies reviewed for FDA to determine critical elements such as the study population characteristics and the composition of the products used. Similarly, the lack of detailed information on studies summarized in review articles and meta-analyses prevents FDA from determining whether the studies are flawed in critical elements such as design, conduct of studies, and data analysis. FDA must be able to review the critical elements of a study to determine whether any scientific conclusions can be drawn from it. Therefore, FDA uses meta-analyses, review articles, and similar publications[8] to identify reports of additional studies that may be useful to the health claim review and as background about the substance-disease relationship. If additional studies are identified, the agency evaluates them individually.

FDA uses animal and *in vitro* studies as background information regarding mechanisms of action that might be involved in any relationship between the substance and the disease. The physiology of animals is different than that of humans. *In vitro* studies are conducted in an artificial environment and cannot account for a multitude of normal physiological processes such as digestion, absorption, distribution, and metabolism that affect how humans respond to the consumption of foods and dietary substances (Institute of Medicine, National Academies of Science, 2005). Animal and *in vitro* studies can be used to generate hypotheses or to explore a mechanism of action but cannot adequately support a relationship between the substance and the disease.

FDA evaluates the individual reports of human studies to determine whether any scientific conclusions can be drawn from each study. The absence of critical factors such as a control group or a statistical analysis means that scientific conclusions cannot be

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[5] In an intervention study, subjects similar to each other are randomly assigned to either receive the intervention or not to receive the intervention, whereas in an observational study, the subjects (or their medical records) are observed for a certain outcome (i.e., disease). Intervention studies provide the strongest evidence for an effect. See Guidance entitled "Significant Scientific Agreement in the Review of Health Claims for Conventional Foods and Dietary Supplements" (December 22, 1999). [http://www.cfsan.fda.gov/~dms/ssaguide.html]

[6] A meta-analysis is the process of systematically combining and evaluating the results of clinical trials that have been completed or terminated (Spilker, 1991).

[7] Review articles summarize the findings of individual studies.

[8] Other examples include book chapters, abstracts, letters to the editor, and committee reports.

drawn from the study (Spilker et al., 1991, Federal Judicial Center, 2000). Studies from which FDA cannot draw any scientific conclusions do not support the health claim relationship, and these are eliminated from further review.

Because health claims involve reducing the risk of a disease in people who do not already have the disease that is the subject of the claim, FDA considers evidence from studies in individuals diagnosed with the disease that is the subject of the health claim only if it is scientifically appropriate to extrapolate to individuals who do not have the disease. That is, the available scientific evidence must demonstrate that: (1) the mechanism(s) for the mitigation or treatment effects measured in the diseased populations are the same as the mechanism(s) for risk reduction effects in non-diseased populations; and (2) the substance affects these mechanisms in the same way in both diseased people and healthy people. If such evidence is not available, the agency cannot draw any scientific conclusions from studies that use diseased subjects to evaluate the substance-disease relationship.

Next, FDA rates the remaining human intervention and observational studies for methodological quality. This quality rating is based on several criteria related to study design (e.g., use of a placebo control versus a non-placebo controlled group), data collection (e.g., type of dietary assessment method), the quality of the statistical analysis, the type of outcome measured (e.g., disease incidence versus validated surrogate endpoint), and study population characteristics other than relevance to the U.S. population (e.g., selection bias and whether important information about the study subjects--e.g., age, smoker vs. non-smoker was gathered and reported). For example, if the scientific study adequately addressed all or most of the above criteria, it would receive a high methodological quality rating. Moderate or low quality ratings would be given based on the extent of the deficiencies or uncertainties in the quality criteria. Studies that are so deficient that scientific conclusions cannot be drawn from them cannot be used to support the health claim relationship, and these are eliminated from further review.

Finally, FDA evaluates the results of the remaining studies. The agency then rates the strength of the total body of publicly available evidence.[9] The agency conducts this rating evaluation by considering the study type (e.g., intervention, prospective cohort, case-control, cross-sectional), the methodological quality rating previously assigned, the quantity of evidence (number of the various types of studies and sample sizes), whether the body of scientific evidence supports a health claim relationship for the U.S. population or target subgroup, whether study results supporting the proposed claim have

[9] See *supra*, note 3.

been replicated,[10] and the overall consistency[11] of the total body of evidence.[12] Based on the totality of the scientific evidence, FDA determines whether such evidence is credible to support the substance/disease relationship, and, if so, determines the ranking that reflects the level of comfort among qualified scientists that such a relationship is scientifically valid.

A. Substance

A health claim characterizes the relationship between a substance and a disease or health-related condition (21 CFR 101.14(a)(1)). A substance means a specific food or component of food, regardless of whether the food is in conventional food form or a dietary supplement (21 CFR 101.14(a)(2)). The petition identified calcium as the substance for the proposed health claims. Calcium, one of the essential nutrients for humans, is a component of milk and milk products (approximately 300 mg per serving) as well as other food sources (e.g., Chinese cabbage, kale, and broccoli) (IOM, 1997). Therefore the agency concludes that the substance, calcium, is a component of food and meets the definition of substance in the health claim regulation (21 CFR 101.14(a)(2)).

B. Disease or Health-Related Condition

A disease or health-related condition means damage to an organ, part, structure, or system of the body such that it does not function properly or a state of health leading to such dysfunctioning (21 CFR 101.14(a)(5)). The petition has identified kidney and urinary stones as the diseases for the proposed claim. Urolithiasis (urinary stones) is a condition that is characterized by the formation or presence of caliculi[13] anywhere along the urinary tract. Nephrolithiasis (kidney stones) is a condition marked by the presence of urinary caliculi within the kidney. The agency concludes that kidney and urinary stones are diseases because in these states, systems of the body are not functioning properly. Therefore, FDA concludes that the petitioner has satisfied the requirement in 21 CFR 101.14(a)(5). In addition, FDA considers kidney stones and urinary stones as the same

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[10] Replication of scientific findings is important for evaluating the strength of scientific evidence (An Introduction to Scientific Research, E. Bright Wilson Jr., pages 46-48, Dover Publications, 1990) and Ioannidis JPA. Contradicted and initially stronger effects in highly cited clinical research. JAMA, 294: 218-228, 2005.

[11] Consistency of findings among similar and different study designs is important for evaluating causation and the strength of scientific evidence (Hill A.B. The environment and disease: association or causation? Proc R Soc Med 1965;58:295-300); See also Systems to rate the scientific evidence, Agency for Healthcare Research and Quality http://www.ahrq.gov/clinic/epcsums/strengthsum.htm#Contents, defining "consistency" as "the extent to which similar findings are reported using similar and different study designs."

[12] See *supra*, note 3.

[13] Caliculi are bud-shaped or cup-shaped structures (Dorland's Illustrated Medical Dictionary, 2003).

disease (i.e., kidney/urinary stones) because the available evidence indicates that the etiology of kidney and urinary stones is the same. [14]

C. Safety Review

Under 21 CFR 101.14(b)(3)(ii), if the substance is to be consumed at other than decreased dietary levels, the substance must be a food or a food ingredient or a component of a food ingredient whose use at levels necessary to justify a claim has been demonstrated by the proponent of the claim, to FDA's satisfaction, to be safe and lawful under the applicable food safety provisions of the Act.

FDA evaluates whether the substance is "safe and lawful" under the applicable food safety provisions of the Act. For dietary supplements, the applicable safety provisions require, among other things, that the dietary ingredient not present a significant or unreasonable risk of illness or injury under conditions of use recommended or suggested in labeling or, if no conditions of use are suggested or recommended in the labeling, under ordinary conditions of use (section 402(f)(1)(A) of the Act (21 U.S.C. 342(f)(1)(A))). Further, a dietary supplement must not contain a poisonous or deleterious substance which may render the supplement injurious to health under the conditions of use recommended or suggested in the labeling (section 402(f)(1)(D) of the Act (21 U.S.C. 342(f)(1)(D))).

The petition stated that calcium is an essential mineral that has a multitude of vital biological roles and also asserted that there is an absolute lack of any reports of clinically significant adverse reactions attributed to dietary calcium. Further, the petition stated that the final rule authorizing the health claim about calcium and osteoporosis concluded that calcium complies with the requirements of 21 CFR 101.14(b)(3)(ii). The petition stated that FDA has determined that ten calcium compounds have been demonstrated to be safe and lawful for use in dietary supplement. 58 FR at 2670 citing 56 FR at 60691. The petition also stated that calcium has prior sanctioned status as safe and lawful under the Act. Further, the petition noted that the North American Menopause Society, in its 2001 Consensus Opinion, stated that the side effect profile from recommended levels of calcium intake is insignificant and that no serious side effects are associated with those levels, and that the Physicians' Desk Reference (PDR) reported that calcium supplements are generally well tolerated.

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[14] Kidney Stones in Adults, National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), National Institutes of Health, U.S. Department of Health and Human Services http://kidney.niddk.nih.gov/kudiseases/pubs/stonesadults/index.htm

It is not necessary for FDA to make a final determination about the safety of calcium in this letter because the agency is denying the proposed claims for lack of credible evidence, as discussed in sections II and III.[15]

II. The Agency's Consideration of a Qualified Health Claim

FDA has identified kidney/urinary stone incidence and hypercalciuria as endpoints to use in identifying kidney/urinary stone risk reduction for purposes of a health claim evaluation. Hypercalciuria[16] is considered a valid surrogate endpoint for kidney/urinary stone disease risk.[17] To evaluate the potential effects of supplemental calcium consumption on kidney/urinary stone risk, FDA considered these endpoints as indicators or predictors of disease.

The petition cited 71 publications as evidence to substantiate the relationship for the proposed claims (see docket No. 2004Q-0102). These publications consisted of 12 review articles, 3 book chapters, 2 Federal Register citations, 1 economic impact study, 1 position paper from the North American Menopause Society, 1 letter to the editor, 3 *in vitro* studies, 16 calcium bioavailability or calcium balance studies, 5 articles on calcium safety, 4 articles on general bone health, 1 article on calcium and osteoporosis, 2 studies on hypertension and nephrolithiasis (kidney stones), and 12 reports of human intervention studies and 8 observational studies that evaluated calcium and kidney stones.

In addition to the studies in your petition that the agency considered, FDA considered 3 additional intervention studies (Heller et al., 2003; Sakhaee et al., 1994; Zerwekh et al., 1988) submitted with comments and 2 reports of observational studies (Curhan et al., 2004; Taylor et al., 2004) identified by FDA from a literature search.

A. Assessment of Review Articles, Meta-Analyses and Abstracts

Although useful for background information, the review articles, meta-analysis, and abstracts do not contain sufficient information on the individual studies which they reviewed and, therefore, FDA could not draw any scientific conclusions from this information. FDA could not determine factors such as the study population characteristics or the composition of the products used (e.g., food, dietary supplement). Similarly, the lack of detailed information on studies summarized in review articles and meta-analyses prevents FDA from determining whether the studies are flawed in critical elements such as design, conduct of studies, and data analysis. FDA must be able to review the critical elements of a study to determine whether any scientific conclusions

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[15] Although not making a determination of safety for purposes of 21 CFR 101.14(b)(3)(ii), the agency notes, as discussed in section II, there are risk considerations that bear on the agency's evaluation of the observational studies in foods submitted in support of the proposed claim for calcium dietary supplements.

[16] Urine calcium (calciuria) above 300 mg per 24 h (men), 250 mg per 24 h (women), or 4 mg/kg per 24 h either sex (Asplin et al., 1998).

[17] See *supra*, note 14.

can be drawn from it. As a result, the review articles supplied by the petitioner do not provide information from which scientific conclusions can be drawn regarding the substance-disease relationships claimed by the petitioner.

B. Assessment of Animal and *In Vitro* Studies

FDA uses animal and *in vitro* studies as background information regarding mechanisms of action that might be involved in any relationship between the substance and the disease, and they can also be used to generate hypotheses or to explore a mechanism of action, but they cannot adequately support a relationship between the substance and the disease in humans. FDA did not consider the *in vitro* studies submitted with the petition as providing any supportive information about the substance - disease relationship because such studies cannot mimic the normal human physiology that may be involved in the risk reduction of kidney/urinary stones, nor can the studies mimic the human body's response to the consumption of calcium. Therefore, FDA cannot draw any scientific conclusions from the *in vitro* studies regarding calcium and the reduction of risk of kidney/urinary stones.

C. Assessment of the Intervention Studies

FDA identified a total of fifteen intervention studies for its review of this qualified health claim (Burtis et al., 1994; Domrongkitchaiporn et al., 2000; Domrongkitchaiporn et al., 2002; Ettinger, 1979; Heller et al., 2003; Nishiura et al., 2002; Sakhaee et al., 1994; Zerwekh et al., 1988; Adams et al., 1979; Dawson-Hughes et al., 1993; Heaney et al., 2001; Ireland and Fordtran, 1973; Jackman et al., 1997; Martini and Wood, 2002; Spencer et al., 1984). These studies were not considered for further review for one or more of the reasons discussed below.

Seven studies did not include a control group for comparing the relative effect of calcium supplementation (Adams et al., 1979; Burtis et al., 1994; Domrongkitchaiporn et al., 2000; Domrongkitchaiporn et al., 2002; Martini and Wood, 2002; Nishiura et al., 2002; Spencer et al., 1984). Therefore, it could not be determined whether changes in the endpoint of interest were due to calcium intake or to unrelated and uncontrolled extraneous factors. Hence, scientific conclusions could not be drawn from these studies (Spilker, 1991).

Zerwekh et al. (1988) measured an outcome (calcium oxalate formation product ratio) that is not recognized as a valid surrogate endpoint for kidney/urinary stones. Therefore, scientific conclusions could not be drawn for evaluating whether calcium intake reduced the risk of kidney/urinary stones.

Heaney et al. (2001) conducted the study for only one day which is not a sufficient duration.[18] Studies must be conducted long enough to determine whether any changes in the endpoint of interest are specifically due to calcium intake. Therefore, scientific conclusions could not be drawn about the relationship between calcium intake and kidney/urinary stones.

Ettinger (1979) evaluated the effect of potassium on kidney stones on subjects with low levels of dietary calcium intake. It did not measure calcium intake or provide calcium as an intervention. Because the study was not designed to evaluate whether calcium intake reduced the risk of kidney/urinary stones, scientific conclusions could not be drawn from this study for the proposed claim.

Three studies did not report a statistical analysis of the data (Ettinger, 1979; Heaney et al., 2001; Spencer et al., 1984). Statistical analysis of the relationship is a critical factor because it provides the comparison between subjects consuming calcium and those not consuming calcium, to determine whether there is a reduction in risk of kidney/urinary stones. When statistical analysis is not performed on the specific substance/disease relationship, it cannot be determined whether there is a difference between the two groups (Spilker, 1991). As a result, these studies provided no information about how calcium may reduce the risk of kidney/urinary stones; hence, no scientific conclusions could be drawn from them.

Three dietary intervention studies provided diets that were high (1 to 2 g/day) or low (0.3 to 0.4 g/day) in calcium to U.S. men and/or women with normal urinary calcium levels and measured the level of calcium in the urine (Heller et al., 2003; Dawson-Hughes et al., 1993; Ireland and Fordtran, 1973). Because the subjects in these 3 studies had normal urinary calcium levels (e.g., not hypercalciuria) at the beginning of the study, it was not possible to evaluate the risk reduction of kidney stones with calcium intake.[19] Therefore, these studies did not provide any scientific evidence about how calcium intake may reduce the risk of kidney/urinary stones; hence, no scientific conclusions could be drawn from them.

Furthermore, the three cross-over studies by Heller et al. (2003), Dawson-Hughes et al. (1993) and Ireland and Fordtran (1973) were *dietary* intervention studies. The petition is for a relationship between calcium supplements and kidney/urinary stones. Unless the test diet is controlled, intervention studies that attempt to evaluate nutrient intake from foods must estimate the levels of the nutrient consumed based on the amount and type of food consumed during the study. The nutrient content of foods can vary (e.g., due to demographics (soil composition), food processing/cooking procedures, or storage

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[18] In order for calciura to be measured properly (i.e., calciuria steady-state levels achieved), urinary calcium should be measured after a minimum of 4 days of dietary calcium intake (Dawson-Hughes et al., 1988).

[19] Since FDA identified hypercalciuria as the only valid surrogate endpoint for kidney stones (see Section II), only a study that evaluated a decrease in the incidence of hypercalciuria could evaluate reduction in risk of kidney stones.

(duration, temperature)). Thus, if the test diet is not controlled for the type and amount of foods consumed, the amount of the nutrient consumed based on reports of dietary consumption may not be accurately ascertained. These studies were not controlled for these factors. Therefore, no scientific conclusions can be drawn from them about the relationship between calcium supplements and kidney/urinary stones.

In addition, foods contain not only calcium, but also other nutrients that may be associated with the metabolism of calcium or the pathogenesis of kidney/urinary stones. Because foods consist of many nutrients and substances, it is difficult to study the nutrient or food components in isolation (Sempos et al., 1999). The role of nutrition in the etiology of kidney/urinary stones is complex. In the case of calcium containing kidney/urinary stones, several macro- and micro-nutrients have been proposed to play a role in both promoting kidney/urinary stones (e.g., sodium, animal protein, carbohydrates, ascorbic acid) and inhibiting kidney/urinary stones (e.g., citrate, potassium, magnesium, phosphorus, fiber, vitamin B6) (Taylor and Curhan, 2004). In addition, food-derived acid load, which is due to the different intestinal absorption rates of relevant food components, especially protein, can lead to acidic urine thereby increasing the risk of kidney/urinary stones (Bihl and Meyers, 2001). Increased risk of kidney/urinary stones is also associated with low urinary output resulting from inadequate fluid intake (Bihl and Meyers, 2001). (See Sempos et al. (1999), Willett (1990), and Willett (1998) regarding the complexity of identifying the relationship between a specific nutrient within a food and a disease). Consequently, for intervention studies on foods, it is not possible to accurately determine whether any observed effects of calcium on kidney/urinary stone risk are due to: 1) calcium alone; 2) interactions between calcium and other nutrients; 3) other nutrients acting alone or together; or, 4) decreased consumption of other nutrients or substances contained in foods displaced from the diet by the increased intake of calcium rich foods unless the studies are controlled so that it can be determined that the effects are from calcium alone, and it is known that there are no confounders. These studies were not controlled. Therefore, scientific conclusions cannot be drawn from these studies about the relationship between calcium supplements and kidney/urinary stones.

Two intervention studies examined the relationship between calcium from dietary supplements and urinary calcium levels (Sakhaee et al., 1994; Jackman et al., 1997). Because the subjects in these 2 studies had normal urinary calcium levels (e.g., not hypercalciuria) at the beginning of the study, it was not possible to evaluate the risk reduction of kidney stones with calcium intake. Therefore, these studies did not provide any scientific evidence about how calcium intake may reduce the risk of kidney/urinary stones; hence, no scientific conclusions could be drawn from them.

D. Assessment of the Observational Studies

FDA identified eight observational studies consisting of three prospective cohort studies[20] published in five separate articles (Curhan et al., 1993; Curhan et al., 1994; Curhan et al., 1997; Curhan et al., 2004; Taylor et al., 2004); two case-control studies[21] (Iguchi et al., 1984; Serio and Fraioli, 1999); two cross-sectional studies[22] (Lemann, Jr. et al., 1996; Leonetti et al., 1998); and one ecological study[23] (Robertson et al., 1979). All eight of these studies estimated calcium intake from diet and the three prospective cohort studies estimated calcium intakes from supplements containing only calcium, as well as calcium from multivitamin sources.

The proposed claim is for a relationship between calcium dietary supplements and a reduced risk of kidney stones. In observational studies that calculate nutrient intake from conventional food, measures of calcium intake are based on recorded dietary intake methods such as food frequency questionnaires, diet recalls, or diet records, in which the type and amount of foods consumed are estimated. A common weakness of observational studies is the limited ability to ascertain the actual food or nutrient intake for the population studied. Furthermore, the nutrient content of foods can vary (e.g., due to demographics (soil composition), food processing/cooking procedures, or storage (duration, temperature)). Thus, it is difficult to ascertain an accurate amount of the nutrient consumed based on reports of dietary intake of foods.

In addition, conventional foods contain not only calcium, but also other nutrients that may be associated with the metabolism of calcium or the pathogenesis of kidney stones. Because foods consist of many nutrients and substances, it is difficult to study the nutrient or food components in isolation (Sempos et al., 1999). For instance, vitamin D regulates calcium absorption and metabolism and sodium and protein increases the urinary excretion of calcium (IOM, 1997). (See Sempos et al. (1999), Willett (1990) and Willett (1998) regarding the complexity of identifying the relationship between a specific nutrient within a food and a disease). For studies based on recorded dietary intake of such foods, it is not possible to accurately determine whether any observed effects of calcium on kidney stone risk were due to: 1) calcium alone; 2) interactions between calcium and other nutrients; 3) other nutrients acting alone or together; or, 4) decreased

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[20] In a cohort study, a group of healthy people or cohort is identified and followed up for a certain time period to ascertain the occurrence of disease and or health related events. (Szklo and Nieto, Epidemiology Beyond the Basics, page 24, Aspen Publishers, 2000).

[21] In a case-control study, a group of cases are identified as the individuals in whom the disease of interest was diagnosed during a given year and controls are selected from individuals who do not have the disease in the same time period (Szklo and Nieto, Epidemiology Beyond the Basics, page 29 Aspen Publishers, 2000).

[22] A cross-sectional study design is a sample of a reference population examined at a given point in time. (Szklo and Nieto, Epidemiology Beyond the Basics, page 38, Aspen Publishers, 2000).

[23] An ecological study examines a possible association between aggregate measure of exposure and disease or mortality (Szklo and Nieto, Epidemiology Beyond the Basics, page 17, Aspen Publishers, 2000).

consumption of other nutrients or substances contained in foods displaced from the diet by the increased intake of calcium-rich foods

In fact, evidence demonstrates that in a number of instances, epidemiological studies based on the recorded dietary intake of conventional foods may indicate a benefit for a particular nutrient with respect to a disease but it is subsequently demonstrated in an intervention study that the nutrient-containing dietary supplement does not confer a benefit or actually *increases* risk of the disease (Lichtenstein and Russell, 2005). For example, previous epidemiological studies reported an association between fruits and vegetables high in beta-carotene and a reduced risk of lung cancer (Peto et al., 1981). However, subsequent intervention studies, the Alpha-Tocopeherol and Beta Carotene Prevention Study (ATBC) and the Carotene and Retinol Efficiency Trial (CARET), demonstrated that beta-carotene supplements increase the risk of lung cancer in smokers and asbestos-exposed workers, respectively (The Alpha-Tocopeherol and Beta Carotene Cancer Prevention Study Group, 1994; Omenn et al., 1996). These studies illustrate that the effect of a nutrient provided as a dietary supplement exhibits different health effects compared to when it is consumed among many other food components. Furthermore, these studies demonstrate the potential public health risk of relying on results from epidemiological studies, in which the effect of a nutrient is based on recorded dietary intake of conventional foods as the sole source for concluding that a relationship exists between a specific nutrient and disease risk; the effect could actually be harmful.

In *Pearson v. Shalala*, the D.C. Circuit noted that FDA had "logically determined" that the consumption of a dietary supplement containing antioxidants could not be scientifically proven to reduce the risk of cancer where the existing research had examined only foods containing antioxidants as the effect of those foods on reducing the risk of cancer may have resulted from other substances in those foods. 164 F.3d 650, 658 (D.C. Cir 1999). The D.C. Circuit, however, concluded that FDA's concern with granting antioxidant vitamins a qualified health claim could be accommodated by simply adding a prominent disclaimer noting that the evidence for such a claim was inconclusive given that the studies supporting the claim were based on foods containing other substances that might actually be responsible for reducing the risk of cancer. *Id.* The court noted that FDA did not assert that the dietary supplements at issue would "threaten consumer's health and safety." *Id.* at 656. There is, however, a more fundamental problem with allowing qualified health claims for nutrients in dietary supplements based solely on studies of foods containing those nutrients than the problem the D.C. Circuit held could be cured with a disclaimer. As noted above, even if the effect of the specific component of the food constituting the dietary supplement could be determined with certainty, recent scientific studies have shown that nutrients in food do not necessarily have the same beneficial effect when taken in the form of a dietary supplement. See Lichtenstein and Russell, 2005. Indeed, not only have studies on single nutrient supplements established that the benefits associated with the dietary intake of certain nutrients do not materialize when the nutrients are taken as a supplement, but some of these studies have actually indicated an *increased* risk for the very disease the nutrients were predicted to prevent.

Id. Thus, an observational study based on food provides no information from which scientific conclusions may be drawn for the single nutrient supplement. Therefore, observational studies in foods do not provide any credible evidence for a claim for risk reduction for a single nutrient supplement because, in fact, the nutrient in supplement form may decrease, have no effect, or actually *increase* risk of the disease or health related condition. For the reasons set forth in Section IV, we have concluded that neither a disclaimer nor qualifying language would suffice to prevent consumer deception in these instances because observational studies in food do not provide credible evidence of risk reduction for a single nutrient supplement.

In this instance, it is not necessary for FDA to determine whether it would be appropriate to consider observational studies on multi-nutrient supplements because, even if it were to consider such studies, they would not change FDA's ultimate conclusion that there is no credible evidence to support the claim as the studies either reported no benefit or *increased* risk of kidney stones. Nonetheless, these studies are summarized below.

Curhan and coworkers (1993) reported results from the Health Professionals Follow-up Study, a prospective cohort study on healthy U.S. male health professionals[24] (n=45,619) with a 4-year follow-up (54±10 years mean age) and 14-year follow up (~64 years mean age) (Taylor et al., 2004). Calcium intake from supplements[25] offered no benefit in reducing the risk of kidney stones (Curhan et al., 1993; Taylor et al., 2004).

There were two prospective cohort studies on healthy U.S. female registered nurses that measured symptomatic kidney/urinary stones. The Nurses' Health Study (n=91,731; 52.7 years mean age) included a 12-year follow-up (Curhan et al., 1997) and the Nurses' Health Study II (n=96,245; 36.7 years mean age) included an 8-year follow-up (Curhan et al., 2004). The Nurses' Health Study reported that calcium intake from supplements[26] offered no benefit and instead showed an *increased* risk for kidney/urinary stones (Curhan et al., 1997). The Nurses' Health Study II reported that calcium from supplements offered no benefit in reducing the risk of kidney stones (Curhan et al., 2004).[27]

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[24] The health professionals consisted of dentists, optometrists, osteopaths, pharmacists, podiatrists, and veterinarians.

[25] Estimation of supplemental calcium intake included intakes from supplements containing only calcium, as well as calcium from multivitamin sources. It is not possible to attribute any observed associations to calcium alone, because of the potential confounding effects from the other vitamins and elements contained in multivitamin supplements and multi-ingredient supplements (i.e., calcium plus some other ingredient(s)).

[26] See *supra*, note 25.

[27] In these three cohorts, increased estimated intakes of dietary calcium were associated with reduced risk for kidney/urinary stones (Curhan, 1997; Curhan et al., 2004; Taylor et al., 2004). However, as stated above, observational studies on foods do not provide scientific information about the relationship between the substance and a reduced risk of kidney stones.

III. Strength of the Scientific Evidence

Below, the agency rates the strength of the total body of publicly available evidence. The agency conducts this rating evaluation by considering the study type (e.g., intervention, prospective cohort, case-control, cross-sectional), the methodological quality rating previously assigned, the quantity of evidence (number of various types of studies and sample sizes), whether the body of evidence supports a health claim relationship for the U.S. population or target subgroup, whether study results supporting the proposed claim have been replicated,[28] and the overall consistency[29] of the total body of evidence. Based on the totality of the scientific evidence, FDA determines whether such evidence is credible to support the substance/disease relationship, and if so, determines the ranking that reflects the level of comfort among qualified scientists that such a relationship is scientifically valid.

As discussed in Section II, there were no intervention or observational studies on hypercalciuria or kidney stone incidence from which FDA could draw scientific conclusions about a relationship between supplemental calcium and kidney/urinary stones. Based on FDA's review of the totality of the scientific evidence, FDA concludes that there is no credible scientific evidence to support a relationship between supplemental calcium intake and risk of kidney/urinary stones.

IV. Agency's Consideration of Disclaimers or Qualifying Language

We considered but rejected use of a disclaimer or qualifying language to accompany the proposed claims. We concluded that neither a disclaimer nor qualifying language would suffice to prevent consumer deception in these instances, where there is no credible evidence to support the claims. Adding a disclaimer or incorporating qualifying language that effectively characterizes the claim as baseless is not a viable regulatory alternative because neither the disclaimer nor the qualifying language can rectify the message conveyed by the unsubstantiated claim. *See, e.g., In re Warner-Lambert Co.*, 86 F.T.C. 1398, 1414 (1975), *aff'd*, 562 F.2d 749 (D.C. Cir. 1977) (pro forma statements of no absolute prevention followed by promises of fewer colds did not cure or correct the false message that Listerine will prevent colds); *Novartis Consumer Health, Inc. v. Johnson & Johnson-Merck Consumer Pharms. Co.*, 290 F.3d 578, 598 (3d Cir. 2002) ("We do not believe that a disclaimer can rectify a product name that necessarily conveys a false message to the consumer."); *Pearson v. Shalala*, 164 F.3d 650, 659 (D.C. Cir 1999) (the court stated that, where the weight of evidence was against the claim, FDA could rationally conclude that the disclaimer "The FDA has determined that no evidence supports this claim" would not cure the misleadingness of a claim). In such a situation, adding a disclaimer or qualifying language does not provide additional information to help consumer understanding but merely contradicts the claim. *Resort Car Rental System, Inc. v. FTC*, 518 F.2d 962, 964 (9th Cir.) (per curiam) (upholding FTC order to

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[28] See *supra*, note 10.
[29] See *supra*, note 11.

excise "Dollar a Day" trade name as deceptive because "by its nature [it] has decisive connotation for which qualifying language would result in contradiction in terms."), *cert denied,* 423 U.S. 827 (1975); *Continental Wax Corp. v. FTC,* 330 F.2d 475, 480 (2d Cir. 1964) (same); *Pasadena Research Labs v. United States,* 169 F.2d 375 (9th Cir. 1948) (discussing "self-contradictory labels"). In the FDA context, courts have repeatedly found such disclaimers ineffective. *See, e.g., United States v. Millpax, Inc.,* 313 F.2d 152, 154 & n.1 (7th Cir. 1963) (disclaimer stating that "no claim is made that the product cures anything, either by the writer or the manufacturer" was ineffective where testimonials in a magazine article promoted the product as a cancer cure); *United States v. Kasz Enters., Inc.,* 855 F. Supp. 534, 543 (D.R.I.) ("The intent and effect of the FDCA in protecting consumers from . . . claims that have not been supported by competent scientific proof cannot be circumvented by linguistic game-playing."), *judgment amended on other grounds,* 862 F. Supp. 717 (1994).

V. Conclusions

Based on FDA's consideration of the scientific evidence and other information submitted with the petition, and other pertinent scientific evidence and information, FDA concludes that there is no credible evidence to support the proposed health claims. Thus, FDA is denying the petition for qualified health claims based on the following proposed health claims:

1. Calcium may reduce the risk of kidney stones.
2. Calcium may reduce the risk of urinary stones.
3. Calcium may reduce the risk of kidney stones and urinary stones.

Please note that scientific information is subject to change, as are consumer consumption patterns. FDA intends to evaluate new information that becomes available to determine whether it necessitates a change in this decision. For example, scientific evidence may become available that will support the use of a qualified health claim or that will support significant scientific agreement for a health claim.

Sincerely,

Barbara Schneeman

Barbara O. Schneeman, Ph.D.
Director
Office of Nutritional Products, Labeling
and Dietary Supplements
Center for Food Safety
and Applied Nutrition

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